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(54) Title: USE OF GASTROINTESTINAL LIPASE INHIBITORS

(57) Abstract

The use of a gastrointestinal lipase inhibitor for the manufacture of oral medicaments for treating or preventing type II diabetes mellitus, and the medicaments thus manufactured.

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Use of gastrointestinal lipase inhibitors

Diabetes mellitus is a condition characterized by an abnormality of glucose utilization and associated with elevation of blood glucose concentration. The most common form of diabetes mellitus is non-insulin dependent diabetes mellitus (NIDDM: Type II). Over 10 million people in the United States alone are affected with type II diabetes mellitus. The initial approach in treating obese patients affected with type II diabetes mellitus is weight reduction. Other types of treatment include oral hypoglycemics and insulin. See, Gregerman, MD, Section 10, Metabolic and Endocrinological Problems, Chapter 72, Diabetes Mellitus, pages 977-989.

The invention relates to the use of a gastrointestinal lipase inhibitor for the manufacture of oral medicaments for treating or preventing type II diabetes mellitus. In another aspect the invention relates to an oral medicament for treating or preventing type II diabetes mellitus characterized in that it contains a gastrointestinal lipase inhibitor. The gastrointestinal lipase inhibitor is preferably tetrahydrolipstatin.

Tetrahydrolipstatin, also known as orlistat, is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making tetrahydrolipstatin.

It has now surprisingly been found that a gastrointestinal lipase inhibitor, preferably tetrahydrolipstatin, when administered orally is useful in the treatment and prevention of type II diabetes mellitus. Preferably, from 60 to 720 mg per day of the gastrointestinal lipase inhibitor are orally administered in divided doses two to three times per day.

Preferred is wherein from 180 to 360 mg, most preferably 360 mg per day of a gastrointestinal lipase inhibitor is administered to a subject, preferably in divided

doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the gastrointestinal lipase inhibitor be administered within about one or two hours of ingestion of a meal containing fat. Generally, for preventing type II diabetes mellitus it is preferred that treatment be administered to 1) a human who has a strong family history of type II diabetes mellitus and has obtained a body mass index of 25 or greater; or 2) a human with impaired glucose tolerance who has obtained a body mass index of 25 or greater. As used herein, the term „strong family history" means a human with at least one first degree relative who has type II diabetes mellitus. Generally, impaired glucose tolerance would be diagnosed by an oral glucose tolerance test.

Tetrahydrolipstatin can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art.

Preferably, tetrahydrolipstatin is administered according to the formulation of Example 1.

EXAMPLE 1

Ingredient	Quantity mg/Capsule
Tetrahydrolipstatin	120.00
Microcrystalline Cellulose (AVICEL PH-101)	93.60
Sodium Starch Glycolate (PRIMOJEL)	7.20
Sodium Lauryl Sulfate	7.20
Polyvinylpyrrolidone (Povidone (K-30))	12.00
Purified Water*	
Talc	0.24
Total	240.24 mg

*Removed during processing

Procedure:

1. Blend tetrahydrolipstatin, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

EXAMPLE 2

Ingredient	Quantity mg/Capsule
Tetrahydrolipstatin	60
Microcrystalline Cellulose	46.8
Sodium Starch Glycolate	3.6
Sodium Lauryl Sulfate	3.6
Polyvinylpyrrolidone	6.0
Purified Water*	
Talc	0.12
Total	120.12 mg

*Removed during processing.

Procedure:

1. Blend tetrahydrolipstatin, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with solution of polyvinyl pyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

EXAMPLE 3

Ingredient	Quantity mg/Capsule	
Tetrahydrolipstatin	60	120
Lactose	40	80
Microcrystalline Cellulose	60	120
Sodium Lauryl Sulfate	5.7	11.4
Sodium Starch Glycolate	20	40
Polyvinylpyrrolidone	10	20
Purified Water*		
Talc	0.2	0.4
Total	195.9 mg	391.8 mg

*Removed during processing.

Procedure:

1. Blend tetrahydrolipstatin, lactose, microcrystalline cellulose and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrollidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder, and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

EXAMPLE 4

Study of Patients with Non-insulin Dependent Diabetes Mellitus:

A one-year double-blind, placebo-controlled study in 321 non-insulin dependent diabetics stabilized on sulfonylureas, was conducted. The results indicate

that 30% of patients treated with tetrahydrolipstatin (120 mg, three-times a day) achieved at least a 5% reduction in baseline body weight compared to 13% of the placebo patients ($p<0.001$). Tetrahydrolipstatin also improved glycemic control in these patients as evidenced by statistically significant reductions in hemoglobin Alc levels (0.5% improvement versus placebo, $p<0.001$) and in doses of sulfonylureas. In this study, 43% of the patients treated with tetrahydrolipstatin were able to reduce or discontinue their oral hypoglycemic medications compared to 29% of the patients receiving placebo, $p<0.01$. Mean levels of fasting glucose remained essentially unchanged compared to baseline in the tetrahydrolipstatin group (-0.02 mmol/L) while there was an increase (+0.54 mmol/L) in the placebo group, $p<0.05$. There were statistically significant improvements in total cholesterol, LDL-cholesterol, LDL/HDL ratio and triglycerides in the group treated with tetrahydrolipstatin compared to placebo.

EXAMPLE 5

Glucose Tolerance in Obese Patients:

Two-year studies that included oral glucose tolerance tests were conducted in obese patients whose baseline oral glucose tolerance test (OGTT) status was either normal, impaired or diabetic. The progression from a normal OGTT as baseline to a diabetic or impaired OGTT following two years of treatment with tetrahydrolipstatin (n=242) (120 mg administered orally three-times a day) or placebo (n=201) were compared. Following treatment with tetrahydrolipstatin, 0.0% and 6.2% of the patients progressed from normal to diabetic and impaired respectively, compared to 1.5% and 12.4% of the placebo treatment group respectively, $p<0.01$. In patients found to have an impaired OGTT at baseline, the percent of patients improving to normal or deteriorating to diabetic status following one and two years of treatment with tetrahydrolipstatin compared to placebo are presented below and the difference between treatment groups was significant:

Baseline OGTT Status Intent-to-treat p pulation	Patients Normal P st-Treatment	Patients Diabetic Post-Treatment
Impaired	one year of treatment	one year of treatment
Placebo n=48	45.8%	10.4%
tetrahydrolipstatin* n=115	72.2%	2.6%
Impaired	2 years of treatment	2 years of treatment
Placebo n=40	47.5%	7.5%
tetrahydrolipstatin** n=60	71.7%	1.7%

* $p<0.01$ and ** $p\leq0.05$, Fisher's Exact Test

Claims

1. Use of a gastrointestinal lipase inhibitor for the manufacture of oral medicaments for treating or preventing type II diabetes mellitus.

2. The use according to claim 1 wherein the gastrointestinal lipase inhibitor is tetrahydrolipstatin.

3. An oral medicament for treating or preventing type II diabetes mellitus characterized in that it contains an effective amount of a gastrointestinal lipase inhibitor.

4. An oral medicament as in claim 3, wherein the gastrointestinal lipase inhibitor is tetrahydrolipstatin.

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INTERNATIONAL SEARCH REPORT

Intern. ..nal Application No
PCT/EP 98/00468

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/00 A61K31/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 638 317 A (HOFFMANN LA ROCHE) 15 February 1995 see page 3, column 14-16; claims 1,2	1-4
Y		1,2

X	US 5 540 917 A (ISLER DOROTHEA ET AL) 30 July 1996 see claims 1-3	3,4
Y		1,2

X	PROUS ET AL: "ORLISTAT" DRUGS OF THE FUTURE, vol. 19, no. 11, - 1994 SPAIN, pages 1003-1010, XP002064254 see page 1008 - page 1009	3,4
A		1,2

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1998	03. 07. 98

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 98/00468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BLOOMGARDEN Z T: "AMERICAN DIABETES ASSOCIATION ANNUAL MEETING 1996: THE ETIOLOGY OF TYPE II DIABETES, OBESITY, AND THE TREATMENT OF TYPE II DIABETES" DIABETES CARE, vol. 19, no. 11, November 1996, pages 1311-1315, XP000654534 see page 1312, right-hand column, line 53-55 ---	1,2
P,X	DATABASE WPI Section Ch, Week 9750 Derwent Publications Ltd., London, GB; Class B04, AN 97-539685 XP002064257 & JP 09 227 398 A (ZERIA SHINYAKU KOGYO KK) , 2 September 1997 see abstract ---	1,3
P,X	HOLLANDERS: "ORLISTAT ENHANCES WEIGHT LOSS IN OBESE PATIENTS WITH DIABETES" AMERICAN FAMILY PHYSICIAN, vol. 56, no. 2, 1997, USA, page 566 XP002064256 see abstract -----	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/00468

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1 ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,3 Partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The wordin gastrointestinal lipase inhibitor is so broad that the search had to be limited for economical reasons

3 ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No
PCT/EP 98/00468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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